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Total synthesis of demethylwedelolactone and wedelolactone by Cu-mediated/Pd(0)-catalysis and oxidative-cyclization

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Abstract

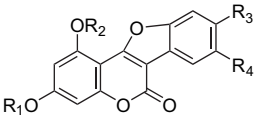
Hedysarimcoumestan **B**, which can be isolated from Chinese herbal medicine, is achieved, in which the longest linear sequence is only eight steps, in 50% overall yield from commercially available phloroglucinol. The key transformations in the synthesis are Cu-mediated/Pd(0)-catalysis and I_2/pyridine oxidative-cyclization reactions. This synthetic strategy can be applied to give access to the demethylwedelolactone (**4**) and wedelolactone (**5**), which were afforded from commercially available phloroglucinol in high 38 and 33% yields, respectively.

Keywords: Hedysarimcoumestans; Demethylwedelolactone; Wedelolactone; Pd-catalysis

1. Introduction

As part of a recent research to prepare new biologically active substances, we were attracted to the coumarin[1] and benzofuran[2] family whose members are widely distributed in biologically important natural products and pharmaceutical agents.[3] Recently, Liang et al.[4] have reported that 10 coumestans were isolated from the roots of *Hedysarum multijugum*, which is a plant in *Hedysarum* Linn. of the family *Leguminosae* used as a folk herbal drug in northwest China. Coumestans comprise a class of naturally occurring products with a variety of biological activities including phytoestrogenic, antibacterial, antifungal, antimyotoxic, and phytoalexine effects.[5] For instance, hedysarimcoumestans, demethylwedelolactone, and wedelolactone are natural products and characteristic members of the coumestan family. These compounds are also important sources of phytoestrogens.[6] In our previous studies,[1,2] we became aware of the facile conversion of coumarins to α-bromocoumarins and the proceeding of Stille coupling of bromocoumarins and stannanes to arylcoumarin skeleton. Therefore, coumestans are ideal targets for the application of these reactions. Although coumestans and wedelolactone (**5**) have been synthesized by several groups,[7] they were achieved with very time-consuming and complicated synthetic approaches. To date, no demethylwedelolactone (**4**) and hedysarimcoumestan **B** (Fig. 1) have been synthesized and deficiently examined the biological activity of the molecules. In addition, to overcome these technical difficulties, we report our studies on the synthesis of hedysarimcoumestan **B** from the commercially available phloroglucinol by Pd-catalyzed coupling and I_2/pyridine oxidative-cyclization reactions.

Perhaps the easiest route to **2** would have been to couple the known 3-bromo-5,7-dimethoxy-2-chromenone[8] and the readily prepared 2-benzyloxy-4-methoxyphenyltributylstannane (**10**),[9] and followed by an oxidative-cyclization reaction.



1 R_1=Me,R_2=R_4=H, R_3=OMe **Hedysarimcoumestan A**
2 R_1=R_2=R_4=H, R_3=OMe **Hedysarimcoumestan B**
3 R_1=R_2=Me, R_3=OMe, R_4=H
4 R_1=R_2=H, R_3=R_4=OH **Demethylwedelolactone**
5 R_1=Me,R_2=H, R_3=R_4=OH **Wedelolactone**

Figure 1. Coumestan natural products of *Hedysarum* Linn.

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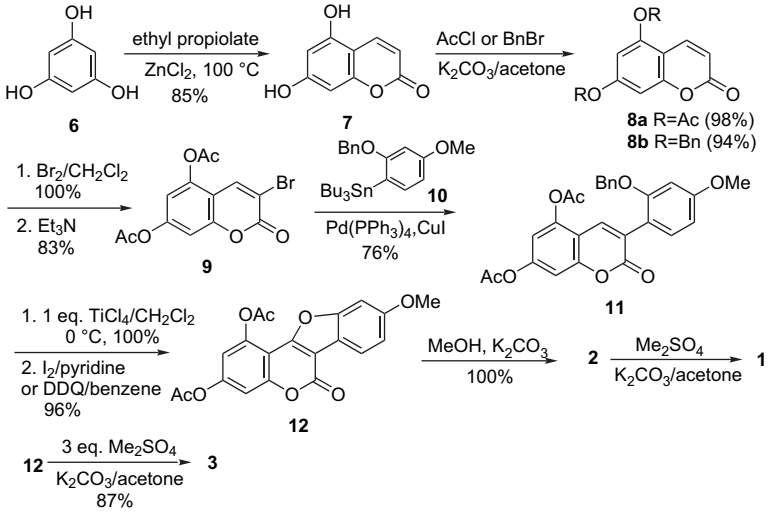
Accordingly, the synthesis of 3-substituted coumarins by the Stille coupling reaction between a bromopyrone and organostannane was reported.[10] In addition, Bauerle et al.[11] have employed Suzuki–Miyaura for the synthesis of 3-substituted coumarins as well. In previous projects[2] we have also achieved such couplings by treating a mixture of benzofuran bromides and aryl stannanes with $Pd(PPh_3)_4$. The reaction is well known as a Pd-catalyzed cross-coupling reaction in a wide variety of transmetalation reagents including Sn, Mg, Zn, B, Al, Zr, and Cu.[12] Herein, we present the first synthesis of the naturally occurring hedysarimcoumestan **B** and demethylwedelolactone (**4**), and this approach allows access to readily provide the wedelolactone (**5**).

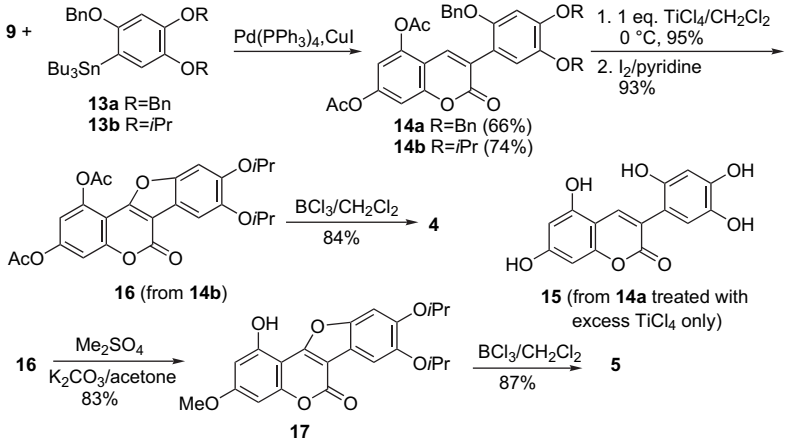
2. Results and discussion

In the beginning of our synthesis, the known coumarin **7** prompted us to prepare the corresponding bromocoumarin **9** from this compound. It was anticipated that **9** was smoothly prepared by our previous method[1] as shown in Scheme 1. Starting with the commercially available phloroglucinol (**6**) and ethyl propiolate, the $ZnCl_2$-catalyzed esterification–cyclization reaction was undergone to provide the coumarin **7** in high 85% yield. 5,7-Dihydroxycoumarin **7** was readily treated with AcCl and BnBr to provide the corresponding acyl- and benzyl-coumarins **8** in excellent 98 and 94% yields, respectively. The following reaction was employed by sequence bromination and dehydrobromination conditions to afford the key intermediate **9** in high yield (two steps 83%). Although we did not know yet if the structure was 3- or 4-bromo coumarin, we did run the methylation reaction of **9** with dimethyl sulfate. ^1H and ^{13}C NMR spectra of the synthetic product are in agreement with those reported for the known 3-bromo-5,7-dimethoxy-2-chromenone.[8] Therefore, this indirectly confirmed that the structure for compound **9** should be 3-bromocoumarin. In case of **9** and **10**, however, the palladium-catalyzed cross-coupling reaction to give **11** was unsuccessful. The major products were the reductive benzyloxyanisole and starting material **9**. This problem would be due its high steric demand, which often slows down the subsequent Sn/Pd transmetalation in the catalytic cycle. Liebeskind et al.[13] have reported that the addition of CuI can increase the reaction rate. Fortunately, the cross-coupling of bromocoumarin **9** with stannane **10** proceeded readily in dioxane by Cu-mediated and Pd(0)-catalysis to give **11** in delighted 76% yield. The resultant arylcoumarin **11** was then transformed into coumestan **12** in two steps. Briefly, it involved removal of the benzyl protecting group with 1 equiv $TiCl_4$, followed by I_2/pyridine or DDQ[14] oxidative-cyclization of the phenol to afford the desired coumestan **12** in excellent 96% yield. It is worth noting that the acyl groups of arylcoumarin **11** were liable to lose under the Lewis acid ($TiCl_4$ and BCl_3) or methanol conditions but survived in limited amount of $TiCl_4$ and short reaction time at low temperature (0 °C). In addition, we failed to obtain the cyclization product **12** under Ag_2O conditions. With precursor **12** in hand, completion of the final steps in the hedysarimcoumestans synthesis was straightforward requiring deacetylation and methylation. Methanolysis of the diacetyl groups in compound **12** provided a quantitative yield of hedysarimcoumestan **B** (**2**). Also, direct methylation of **12** with 3 equiv Me_2SO_4 obtained the expected product **3** in high 87% yield, and conversion of **2** with 1 equiv Me_2SO_4 gave the desired hedysarimcoumestan **A** (**1**) in high 81% yield as well. Melting points and ^1H and ^{13}C NMR spectra of the synthetic products are in agreement with those reported for the naturally derived materials.[4]

It is worth noting that our synthetic strategy can be applied in the syntheses of **4** and **5**. The syntheses of **4** and **5** were achieved by using the same strategy that utilized the Liebeskind coupling conditions and I_2/pyridine oxidative-cyclization reactions described above. The reaction of bromocoumarin **9** with stannane **13** was readily converted to obtain the corresponding arylcoumarin **14** in satisfied yield between 66 and 74%. At this point, the final step of the demethylwedelolactone (**4**) synthesis was focused on the sequence deprotection and oxidative-cyclization reaction of **14a**. Like



Scheme 1.



Scheme 2.

previous debenzylation of **11**, similarly **14a** can readily be converted with 5 equiv $TiCl_4$ at 0 °C to give the desired intermediate pentahydroxyl arylcoumarin **15**, but the catechol **15** was unstable under vacuum and acid conditions during isolation. With the aim of developing a successful route to **4**, we then sought to selectively deprotect only the required 2′-benzyl group of **14**. Therefore, **14b** smoothly proceeded the removal of the benzyl protecting group with 1 equiv $TiCl_4$ at 0 °C in excellent 95% yield, followed by I_2/pyridine oxidative-cyclization of the hydroxylarylcoumarin to afford the anticipated coumestan **16** in excellent 93% yield (Scheme 2). The structure of 3-aryl coumarin **14b** was assigned by X-ray crystallographic methods.[15] Also, it is worth noting that the structure of 3-bromocoumarin **9** can be proved indirectly. Furthermore, the key precursor **16** readily carried out the deprotection with BCl_3 at 0 °C to generate the demethylwedelolactone (**4**) in high 84% yield. Finally, 5,7-acetoxycoumestan **16** was transformed by the selective methylation with 1 equiv Me_2SO_4 and followed by the deprotection with 2 equiv BCl_3 to provide the desired product **5** in high 72% yield (over two steps).

3. Conclusion

In summary, a concise route to hedysarimcoumestan **B** (**2**) has been achieved, in which the longest linear sequence is only eight steps, in 50% overall yield from commercially available phloroglucinol. This synthesis is high yielding and easily applied to give access to a variety of different hedysarimcoumestan **A** (**1**) and coumestan analogues, especially, demethylwedelolactone (**4**) and wedelolactone (**5**), which were afforded from commercially available phloroglucinol in high 38 and 33% yields, respectively. In addition, it demonstrated the usefulness of the Pd-catalyzed coupling reaction with CuI-mediated for 3-aryl-2-coumarin synthesis. Finally, the versatile I_2/pyridine is demonstrated by the oxidative-cyclization to optionally afford the desired furan products for acid sensitive substrates. Further biological assays are currently underway to evaluate the efficacy of these compounds as pharmaceutical agents.

4. Experimental[1]

4.1. 5,7-Dihydroxychromen-2-one (7)

This compound was prepared as a white solid from phloroglucinol and ethyl propiolate according to the procedure of Kaufman and Kelly;[16] mp 274–275 °C (lit.[16] mp 280 °C). ^{1}H NMR (DMSO-d_6) δ 6.02 and 7.95 (d, J=9.6 Hz, 2H), 6.18 and 6.26 (d, J=1.8 Hz, 2H), 10.38 and 10.66 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 94.4, 98.6, 102.1, 109.0, 140.0, 156.3, 156.8, 161.2, 162.5.

4.2. 5,7-Diacetoxychromen-2-one (8a)

A mixture of **7** (5.00 g, 28.0 mmol) and K_2CO_3 (19.40 g, 140.4 mmol) in dry acetone was heated to reflux (oil bath 90 °C) for 1 h, and added acetyl chloride (8.0 mL, 112.3 mmol) dropwise with syringe. The reaction suspension was stirred for 1.5 h at 90 °C, and the resulting solution was cooled down and filtrated out of the excess K_2CO_3. The solvent was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with CH_2Cl_2 to give compound **8a** (7.20 g, 98%) as a white solid; mp 134–135 °C (lit.[17] mp 124–125 °C).

4.3. 5,7-Dibenzyloxychromen-2-one (8b)

The **8b** was prepared, using above procedure, from **7** (0.50 g, 0.3 mmol) and K_2CO_3 (0.85 g, 6.2 mmol) with benzyl bromide (0.7 mL, 5.9 mmol). The solvent was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with hexane/CH_2Cl_2 (2:1) to give compound **8b** (0.95 g, 94%) as a white solid; mp 132–133 °C (lit.[18] mp 137–138 °C).

4.4. 3-Bromo-5,7-diacetoxychromen-2-one (9)

To a solution of **8a** (2.00 g, 7.6 mmol) in CH_2Cl_2 (50.0 mL) was added Br_2 (0.7 mL, 13.6 mmol) dropwise into the solution at 0 °C for 8 h. The brown solution was extracted with CH_2Cl_2

(2×100.0 mL). The organic layer concentrated in vacuo afforded dibromochromanone (3.20 g, 100%). To the dibromide in CH_2Cl_2 was added Et_3N at room temperature, and then stirred for 2 h. The resulting solution was removed from the solvent in vacuo and the residue was purified by flash chromatography on silica gel with hexane/CH_2Cl_2 (2:1) to give **9** (2.15 g, 83%) as a white solid; mp 146–147 °C. ^{1}H NMR ($CDCl_3$) δ 2.33 and 2.43 (s, 6H), 7.03 and 7.05 (d, J=2.1 Hz, 2H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.1, 107.8, 110.8, 111.6, 112.6, 138.1, 146.3, 152.9, 153.9, 156.2, 167.9, 168.1; HRMS (EI) calcd for $C_{13}H_9BrO_6$ (M^+) 339.9583, found 339.9584. Anal. Calcd for $C_{13}H_9BrO_6$: C, 45.77; H, 2.66; O, 28.14. Found: C, 45.62; H, 2.43; O, 28.30.

4.5. 3-Bromo-5,7-dimethoxychromen-2-one

To a mixture of **9** (0.24 g, 0.7 mmol) and K_2CO_3 (0.30 g, 2.1 mmol) in acetone (5.0 mL) was added Me_2SO_4 (0.20 mL, 2.1 mmol) at room temperature, and then refluxed at 70 °C for 1 h by TLC monitoring. After cooling, the solution was evaporated in vacuo, and the brown solid was subjected to flash chromatography (SiO_2, CH_2Cl_2/EtOAc 1:1) to give 3-bromo-5,7-dimethoxychromen-2-one (0.20 g, 0.7 mmol) in 100% yield.

4.6. 2-Benzyloxy-4-methoxyphenyltributylstannane (*10*)

The stannane **10** was prepared, using the previous procedure,[9] from the known[19] 2-benzyloxy-4-methoxyphenyl bromide (1.00 g, 3.4 mmol). The product **10** was isolated in 99% yield (1.70 g, 3.4 mmol) as a colorless oil. ^{1}H NMR [$(CD_3)_2CO$] δ 0.81 (t, J=6.6 Hz, 9H), 0.94 (t, J=6.6 Hz, 6H), 1.21–1.31 (m, 6H), 1.40–1.50 (m, 6H), 3.75 (s, 3H), 5.06 (s, 2H), 6.53 (dd, J=7.8, 2.1 Hz, 1H), 6.57 (d, J=2.1 Hz, 1H), 7.22 (d, J=7.8 Hz, 1H), 7.33–7.48 (m, 5H); ^{13}C NMR [$(CD_3)_2CO$] δ 9.3, 13.0, 27.1, 28.9, 54.5, 69.7, 98.2, 105.7, 119.5, 127.8, 127.9, 128.3, 137.1, 137.3, 162.0, 164.2.

4.7. 5,7-Diacetoxy-3-(2-benzyloxy-4-methoxyphenyl)-chromen-2-one (*11*)

A mixture of bromocoumarin **9** (0.20 g, 0.6 mmol), CuI (0.02 g, 20 mol %), tetrakis(triphenylphosphine)palladium(0) (0.07 g, 10 mol %), and stannane **10** (0.38 g, 0.8 mmol) were introduced into a sealable tube containing anhydrous dioxane (5.0 mL), and the reaction mixture degassed. The tube was sealed and heated for 12 h at 160 °C, after cooling, and the solution was filtered and evaporated in vacuo. The filtrate residue was subjected to flash chromatography (SiO_2, CH_2Cl_2/hexane 3:2) to provide the desired **11** (0.21 g, 76%) as a yellow solid; mp 141–145 °C. ^{1}H NMR [$(CD_3)_2CO$] δ 2.29 and 2.32 (s, 6H), 3.81 (s, 3H), 5.14 (s, 2H), 6.60 (dd, J=8.4, 2.4 Hz, 1H), 6.72 and 7.00 (d, J=2.1 Hz, 2H), 7.08 (d, J=2.4 Hz, 1H), 7.33 (d, J=8.4 Hz, 1H), 7.27–7.45 (m, 5H), 7.95 (s, 1H); ^{13}C NMR [$(CD_3)_2CO$] δ 20.2, 20.4, 55.2, 70.4, 100.2, 105.3, 107.6, 111.6, 112.8, 117.2, 126.0, 127.6, 127.9, 128.7, 132.0, 134.9, 137.5, 147.9, 152.8, 154.6, 157.8, 159.2, 161.9, 168.5, 168.7; HRMS (EI) calcd for $C_{27}H_{22}O_8$ (M^+) 474.1315, found 474.1318.

4.8. 1,3-Diacetoxy-9-methoxy-benzo[4,5]furo[3,2-c]-chromen-6-one (*12*)

To a solution of **11** (0.20 g, 0.4 mmol) in CH_2Cl_2 (10.0 mL) was added $TiCl_4$ (0.04 mL, 0.4 mmol) dropwise at 0 °C for 10 min. The reaction was monitored by TLC and quenched by treatment with ice water. The solvent was removed and the residue was subjected to flash chromatography (SiO_2, CH_2Cl_2/EtOAc 20:1) to give the desired hydroxyaryl coumarin (0.16 g, 100%) as a yellow solid; mp 191–192 °C. ^{1}H NMR ($CDCl_3$) δ 2.34 and 2.41 (s, 6H), 3.83 (s, 3H), 6.60 and 7.06 (d, J=2.1 Hz, 2H), 6.61 and 7.16 (d, J=5.1 Hz, 2H), 7.20 (s, 1H), 7.68 (br s, 1H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.1, 55.5, 104.1, 107.6, 108.3, 111.3, 112.8, 115.3, 126.6, 131.6, 135.7, 147.3, 152.6, 153.5, 156.4, 162.4, 162.8, 168.1, 168.2; HRMS (EI) calcd for $C_{20}H_{16}O_8$ (M^+) 384.0845, found 384.0848. I_2 (1 equiv 0.4 mmol) or DDQ (0.12 g, 0.6 mmol) was added to a solution of the synthetic hydroxyaryl coumarin (0.15 g, 0.4 mmol) in anhydrous pyridine (15.0 mL) or benzene (15.0 mL) at ambient temperature. The mixture was heated for refluxing at 110 °C (oil bath) for 15 h. After cooling, the solution was evaporated in vacuo and the brown solid was subjected to flash chromatography (SiO_2, CH_2Cl_2/EtOAc 20:1). The coumestan **12** (0.14 g, 96%) was isolated as a white solid; mp 246–247 °C. ^{1}H NMR ($CDCl_3$) δ 2.36 and 2.55 (s, 6H), 3.92 (s, 3H), 6.99 and 7.23 (d, J=2.1 Hz, 2H), 7.08 and 7.98 (d, J=9.3 Hz, 2H), 7.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.2, 55.9, 96.5, 105.7, 106.4, 108.8, 113.3, 114.0, 115.6, 122.1, 145.5, 152.2, 153.9, 156.6, 156.8, 157.3, 159.9, 168.3, 169.0; HRMS (EI) calcd for $C_{20}H_{14}O_8$ (M^+) 382.0689, found 382.0687.

4.9. Hedysarimcoumestan ***B*** (*2*)

A mixture of **12** (0.050 g, 0.1 mmol) and K_2CO_3 (0.083 g, 0.6 mmol) in MeOH (3.0 mL) was refluxed at 70 °C (oil bath) for 30 min. The resulting reaction mixture was cooled down and neutralized with 1 M HCl and extracted with EtOAc (3×5.0 mL). The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (SiO_2, MeOH/EtOAc 1:5) to obtain **2** (0.039 g, 100%) as a white solid; mp>300 °C (lit.[4] mp>300 °C). ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 6.42 and 6.46 (d, J=2.1 Hz, 2H), 7.10 (dd, J=8.4, 2.1 Hz, 1H), 7.53 (d, J=2.1 Hz, 1H), 7.79 (d, J=8.4 Hz, 1H), 10.58 and 11.02 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 56.9, 96.0, 96.2, 98.2, 100.2, 101.6, 114.3, 116.7, 121.2, 156.4, 156.7, 156.8, 158.8, 159.5, 161.4, 162.7; HRMS (ESI) calcd for $C_{16}H_{10}O_6$ (neg) 298.0477, found 298.0462.

4.10. Hedysarimcoumestan ***A*** (*1*)

Coumestan **2** (0.030 g, 0.1 mmol) was dissolved in acetone (4.0 mL). Me_2SO_4 (16.1 μL, 0.1 mmol) and K_2CO_3 (0.020 g,

0.2 mmol) were added and the suspension was heated at 70 °C for 1 h. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc 1:1) to give **1** (0.025 g, 81%) as a white solid; mp>300 °C (lit.[4] mp>300 °C). ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 3.85 and 3.89 (s, 6H), 6.54 (br s, 2H), 7.03 (dd, J=8.4, 2.1 Hz, 1H), 7.24 (d, J=2.1 Hz, 1H), 7.91 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 54.6, 54.7, 92.2, 95.8, 95.9, 97.5, 100.8, 112.0, 115.0, 119.6, 154.2, 154.7, 155.2, 157.3, 157.6, 159.3, 161.8; HRMS (ESI) calcd for $C_{17}H_{12}O_6$ (neg) 312.0634, found 312.0623.

4.11. 1,3,9-Trimethoxy-benzo[4,5]furo[3,2-c]chromen-6-one (3)

From **12** (0.03 g, 0.07 mmol) and Me_2SO_4 (32.0 μL, 0.2 mmol) with K_2CO_3 (0.020 g, 0.2 mmol), using above procedure, the coumestan **3** (0.02 g, 87%) was isolated as a white solid; mp 220–222 °C (lit.[4] mp 220–225 °C). ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 3.90 and 4.05 (s, 9H), 6.46 and 6.60 (d, J=2.1 Hz, 2H), 7.03 (dd, J=8.7, 2.1 Hz, 1H), 7.22 (d, J=2.1 Hz, 1H), 7.87 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 55.2, 55.3, 55.7, 93.1, 94.9, 96.1, 97.1, 102.0, 112.7, 115.3, 120.3, 155.2, 155.7, 156.0, 157.7, 158.3, 159.2, 162.4; HRMS (EI) calcd for $C_{18}H_{14}O_6$ (M^+) 326.0790, found 326.0789.

4.12. 2-Benzyloxy-4,5-dibenzyloxyphenyltributylstannane (13a)

The stannane **13a** was prepared, using the previous procedure,[9] from the 2,4,5-tribenzyloxyphenyl bromide (1.00 g, 2.1 mmol) in 96% yield (1.39 g, 2.0 mmol) as a colorless oil. ^{1}H NMR [$(CD_3)_2CO$] δ 0.82 (t, J=7.5 Hz, 9H), 0.95 (t, J=7.8 Hz, 6H), 1.21–1.29 (m, 6H), 1.41–1.50 (m, 6H), 5.02, 5.07, and 5.17 (s, 6H), 6.88 and 6.97 (s, 2H), 7.30–7.51 (m, 15H); ^{13}C NMR [$(CD_3)_2CO$] δ 9.4, 13.2, 27.1, 29.0, 70.4, 70.7, 72.4, 99.7, 119.5, 125.1, 127.5, 127.6, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.4, 137.5, 137.7, 138.3, 143.2, 150.9, 158.5.

4.13. 2-Benzyloxy-4,5-diisopropyloxyphenyltributylstannane (13b)

The product **13b** was isolated from the 2-benzyloxy-4,5-diisopropyloxyphenyl bromide (1.00 g, 2.6 mmol) in 94% yield (1.46 g, 2.5 mmol) as a colorless oil. ^{1}H NMR [$(CD_3)_2CO$] δ 0.97 (t, J=8.1 Hz, 9H), 1.06 (t, J=7.8 Hz, 6H), 1.21 and 1.25 (d, J=6.3 Hz, 12H), 1.21–1.32 (m, 6H), 1.39–1.55 (m, 6H), 4.30 and 4.56 (hept, J=6.3 Hz, 2H), 5.03 (s, 2H), 6.67 and 6.70 (s, 2H), 7.31–7.47 (m, 5H); ^{13}C NMR [$(CD_3)_2CO$] δ 9.3, 13.0, 21.6, 21.7, 27.0, 28.9, 70.2, 70.8, 72.6, 101.5, 119.4, 127.6, 127.7, 128.2, 128.3, 137.5, 142.8, 150.8, 158.6.

4.14. 5,7-Diacetoxy-3-(2,4,5-tribenzyloxyphenyl)chromen-2-one (14a)

From bromocoumarin **9** (0.20 g, 0.6 mmol) and **13a** (0.60 g, 0.9 mmol), **14a** was obtained in 66% (0.25 g, 0.4 mmol) yield as a yellow solid; mp 141–142 °C. ^{1}H NMR ($CDCl_3$) δ 2.24 and 2.32 (s, 6H), 4.95, 5.12, and 5.14 (s, 6H), 6.68 and 7.10 (s, 2H), 6.95 and 7.02 (d, J=1.8 Hz, 2H), 7.25–7.46 (m, 15H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.1, 71.5, 71.7, 72.6, 102.6, 107.5, 111.0, 112.0, 116.4, 118.8, 125.0, 127.2, 127.3, 127.6, 127.8, 127.9, 128.0, 128.4, 128.5, 128.6, 135.0, 136.7, 136.8, 137.2, 142.9, 147.0, 150.5, 151.5, 152.1, 154.2, 159.7, 168.1, 168.4; HRMS (EI) calcd for $C_{40}H_{32}O_9$ (M^+) 656.2046, found 656.2048.

4.15. 5,7-Diacetoxy-3-(2-benzyloxy-4,5-diisopropyloxyphenyl)chromen-2-one (14b)

Compound **14b** was prepared from **9** (0.20 g, 0.6 mmol) and **13b** (0.52 g, 0.9 mmol) in 74% (0.24 g, 0.4 mmol) yield as a yellow-green crystal; mp 158–159 °C. ^{1}H NMR ($CDCl_3$) δ 1.32 and 1.33 (d, J=6.3 Hz, 12H), 2.24 and 2.31 (s, 6H), 4.36 and 4.51 (hept, J=6.3 Hz, 2H), 5.04 (s, 2H), 6.64 and 7.01 (s, 2H), 6.96 and 7.03 (d, J=2.1 Hz, 2H), 7.27–7.40 (m, 5H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.1, 22.1, 22.3, 71.5, 72.1, 73.6, 104.3, 107.5, 111.1, 112.0, 116.5, 122.2, 125.2, 127.2, 127.8, 128.5, 134.9, 136.8, 142.6, 147.0, 150.9, 151.8, 152.0, 154.2, 159.7, 168.2, 168.4. Anal. Calcd for $C_{32}H_{32}O_9$: C, 68.56; H, 5.75; O, 25.69. Found: C, 68.34; H, 5.69; O, 25.77.

4.16. 5,7-Dihydroxy-3-(2,4,5-trihydroxyphenyl)chromen-2-one (15)

Compound **15** was prepared, using above procedure, from **14a** (0.15 g, 0.2 mmol) and $TiCl_4$ (0.11 mL, 1.1 mmol) in 56% yield (0.04 g, 0.1 mmol) as a yellow solid. ^{1}H NMR [$(CD_3)_2CO$] δ 6.32 and 6.38 (d, J=2.1 Hz, 2H), 6.46 and 6.85 (s, 2H), 8.07 (s, 1H), 7.51, 7.77, 7.96, 9.36, and 9.65 (br s, 5H).

4.17. 1,3-Diacetoxy-8,9-diisopropyloxy-benzo[4,5]furo-[3,2-c]chromen-6-one (16)

The **14b** (0.30 g, 0.5 mmol) was transformed, using the general procedure, to generate the corresponding hydroxyaryl coumarin (0.24 g, 0.5 mmol) in 95% yield as a yellow solid; mp 165–166 °C. ^{1}H NMR ($CDCl_3$) δ 1.30 and 1.44 (d, J=6.3 Hz, 12H), 2.34 and 2.41 (s, 6H), 4.31 and 4.56 (hept, J=6.3 Hz, 2H), 6.61 and 6.86 (s, 2H), 7.05 and 7.13 (d, J=2.1 Hz, 2H), 7.47 (br s, 1H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.1, 22.0, 22.2, 71.1, 74.4, 106.4, 107.5, 111.2, 112.8, 114.0, 123.2, 126.4, 135.8, 142.2, 147.2, 151.1, 152.5, 152.7, 153.4, 162.7, 168.2, 168.3; HRMS (EI) calcd for $C_{25}H_{26}O_9$ (M^+) 470.1577, found 470.1585. Following oxidative-cyclization with I_2 (1 equiv 0.5 mmol), coumestan **16** was isolated in 93% yield (0.22 g, 0.5 mmol) as

a white solid; mp 223–224 °C. ^{1}H NMR ($CDCl_3$) δ 1.40 and 1.41 (d, J=6.3 Hz, 12H), 2.35 and 2.54 (s, 6H), 4.57 and 4.58 (hept, J=6.3 Hz, 2H), 6.98 and 7.22 (d, J=2.1 Hz, 2H), 7.13 and 7.59 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.1, 22.0, 22.1, 72.8, 73.1, 101.2, 105.8, 106.5, 108.5, 108.8, 113.2, 115.8, 145.4, 148.4, 149.7, 150.8, 152.0, 153.7, 156.5, 157.5, 168.3, 169.0; HRMS (EI) calcd for $C_{25}H_{24}O_9$ (M^+) 468.1420, found 468.1423.

4.18. Demethylwedelolactone (*4*)

To a solution of **16** (0.10 g, 0.2 mmol) in CH_2Cl_2 (5.0 mL) was added BCl_3 (0.4 mL, 1.0 M) dropwise at 0 °C. The reaction was monitored by TLC and quenched by treatment with MeOH. The solvent was removed and the residue was subjected to flash chromatography (SiO_2, EtOAc/MeOH 10:1) to give **4** (0.05 g, 84%) as a yellow solid; mp 305 °C (dec) (lit.[7a] mp>330 °C). ^{1}H NMR [$(CD_3)_2CO$] δ 6.44 and 6.45 (d, J=2.1 Hz, 2H), 7.17 and 7.38 (s, 2H), 8.35, 8.36, 9.35, and 9.60 (br s, 4H); ^{13}C NMR [$(CD_3)_2CO$+DMSO-d_6] δ 95.1, 95.8, 98.5, 99.3, 101.4, 104.8, 114.7, 144.2, 145.2, 149.3, 155.4, 155.9, 158.0, 159.9, 161.5; HRMS (EI) calcd for $C_{15}H_8O_7$ (M^+) 300.0270, found 300.0272.

4.19. 1-Hydroxy-3-methoxy-8,9-diisopropyloxy-benzo[4,5]-furo[3,2-c]chromen-6-one (*17*)

The methylation reaction was employed, using above procedure, from **16** (0.10 g, 0.2 mmol) and Me_2SO_4 (32.0 μL, 0.2 mmol) with K_2CO_3 (0.04 g, 0.3 mmol). Compound **17** was isolated in 83% yield (0.07 g, 0.2 mmol) as a white solid; mp 194–195 °C. ^{1}H NMR ($CDCl_3$) δ 1.39 and 1.40 (d, J=6.0 Hz, 12H), 3.87 (s, 3H), 4.52 and 4.58 (hept, J=6.0 Hz, 2H), 6.49 and 6.61 (d, J=1.5 Hz, 2H), 7.23 and 7.57 (s, 2H); ^{1}H NMR [$(CD_3)_2CO$+DMSO-d_6] δ 1.33 and 1.35 (d, J=6.3 Hz, 12H), 3.86 (s, 3H), 4.55 and 4.67 (hept, J=6.3 Hz, 2H), 6.51 and 6.52 (d, J=2.1 Hz, 2H), 7.35 and 7.43 (s, 2H); ^{13}C NMR [$(CD_3)_2CO$+DMSO-d_6] δ 21.4, 21.6, 55.3, 71.8, 72.5, 93.1, 96.9, 98.3, 100.8, 102.0, 108.5, 116.0, 147.4, 148.8, 150.5, 155.5, 156.0, 157.7, 160.2, 163.0; HRMS (EI) calcd for $C_{22}H_{22}O_7$ (M^+) 398.1366, found 398.1360.

4.20. Wedelolactone (*5*)

From **17** (0.12 g, 0.3 mmol) and BCl_3 (0.7 mL, 1.0 M), **5** was achieved in 87% (0.08 g, 0.3 mmol) yield as a yellow solid; mp 300 °C (dec) (lit.[5] mp 300 °C (dec)). ^{1}H NMR [$(CD_3)_2CO$+DMSO-d_6] δ 3.90 (s, 3H), 6.51 and 6.53 (s, 2H), 7.17 and 7.37 (s, 2H), 8.81, 8.85, and 10.56 (br s, 3H); ^{13}C NMR [$(CD_3)_2CO$+DMSO-d_6] δ 55.3, 93.0, 97.0, 98.3, 98.5, 102.2, 104.8, 114.5, 144.3, 145.5, 149.5, 155.2, 155.8, 157.8, 159.4, 162.7; HRMS (EI) calcd for $C_{16}H_{10}O_7$ (M^+) 314.0427, found 314.0425.

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